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DESMOPRESSIN PREVENTS IMMERSION DIURESIS AND IMPROVES PHYSICAL PERFORMANCE AFTER LONG DURATION DIVES

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14. ABSTRACT
Water immersion causes dehydration affecting blood flow to muscle, skin and reduces blood volume. Desmopressin inhibits urine production preventing immersion-induced blood volume loss. This study had two goals 1) examine the effect of Desmopressin on immersion diuresis and 2) any subsequent effects on physical and cognitive performance. Twenty U.S. Navy divers participated in a pool study (72°F) and field study (80-82°F) for 3.5 h at 10-15 feet of seawater; each completed a control and experimental dive. Hydration and performance were measured. Before the experimental dive, subjects received 40 μg of Desmopressin intranasally. Before and after each dive blood samples were taken, performance assessments were performed, and urine, electrolyte and hematologic values were determined. Desmopressin reduced immersion diuresis while maintaining post dive physical performance. Desmopressin significantly attenuated immersion diuresis and maintained aerobic capacity during 3.5 h dives in warm water.

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dehydration, 1-Desamino-8-D-Arginine Vasopressin, blood flow, urine output, serum osmolality

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ABSTRACT

Introduction: Water immersion causes a relocation of blood volume and increased urine production resulting in a loss of plasma volume (dehydration). Dehydration affects blood flow to muscle, skin and reduces blood volume. Desmopressin (1-Desamino-8-D-Arginine Vasopressin), an analog of endogenous vasopressin, inhibits urine production preventing immersion-induced blood volume loss.

Methods: This study had two goals 1) examine the effect of Desmopressin on immersion diuresis and 2) any subsequent effects on physical and cognitive performance. Twenty U.S. Navy divers participated in long duration air dives, 10 in a pool study (72°F) and 10 in a field study (80-82°F). Hydration and physical and cognitive performance were measured. Dives lasted 3.5 h at 10-15 feet of seawater (fsw). Each subject completed a control and experimental dive. During the experimental dive, subjects received 40 μg of Desmopressin intranasally before entering the water. Before and after each dive blood samples were taken and exercise and cognitive performance assessments were performed. Urine, electrolyte and hematologic values were determined pre and post-dive. Changes in body weight were also measured.

Results: Desmopressin reduced immersion diuresis demonstrated by urinary output and weight reduction while maintaining post dive physical performance. Serum osmolality was unchanged while total urine volume decreased 60% in the pool (1867 $\pm$ 187 ml to 663 $\pm$ 142 ml) and 75% in the field (1355 $\pm$ 301 ml to 290 $\pm$ 57 ml). Cognitive performance was unchanged.

Conclusions: Desmopressin significantly attenuated immersion diuresis and maintained aerobic capacity during 3.5 h dives in warm water.

INTRODUCTION

Military operational diving missions are often long. A common complaint of divers after these dives is a sense of extreme physical fatigue and loss of mental acuity (13). Compromised acuity and fatigue are hazardous for the diver in a combat zone. This fatigue is reported to be more profound than what would be experienced if exercising the same amount on the surface. It is caused by two factors: hypothermia and immersion diuresis (1,15,16,17,19,21). Water immersion increases the rate of fluid loss by increasing the rate of urine production (16). For exposures lasting longer than 2 h fluid shifts and losses elicited by immersion will cause dehydration and decrease blood volume (7). Desmopressin (1-desamino-8-D-arginine vasopressin), an analog of endogenous vasopressin, has been shown to reduce immersion diuresis by up to 80% (15). Fluid loss and dehydration results in impaired physical performance, both during short-term high intensity efforts and endurance activity (2, 19). One study examined the effects of immersion diuresis on divers' physical performance and observed an average fluid loss of approximately 1.3 liters after a 195 min dive at 10-30 feet of seawater (fsw) (10). The average increase in heart rate (HR) after a standard exercise test (Harvard step test) was 12 ± 2 beats per minute (bpm). In another field study, Desmopressin at a 20μg dose was used on morning and night training dives in the open ocean. A maintained aerobic performance with Desmopressin was noted only after the night dives (11). Physiological Work Capacity 170 (PWC-170), a test that estimates aerobic capacity, has shown a decline in exercise capacity during cold water immersions (12).

The assessment of cognitive function following Desmopressin administration considered that diving-induced changes in vasopressin levels might affect optimal performance capabilities. Administration of Desmopressin improved both acquisition and memory capabilities in humans

with compromised levels of vasopressin (9). Vasopressin is an active modulator of cognitive function in vertebrates. Binding sites are located in limbic structures associated with cognitive function, including the hippocampus, and reduced levels in the limbic system are associated with degradation in cognitive function (8). Additionally, intranasal administration of Desmopressin improves recall and memory in man (3).

This investigation exposed U.S. Navy divers to complete immersion in both a controlled and field setting. We observed changes in physical and cognitive performance, and various markers of hydration status. It was our goal to preserve diver hydration and increase physical and cognitive performance.

The specific questions this study addressed are:

1. Will intranasal administration of 40 μm of Desmopressin significantly reduce dehydration?
2. Will Desmopressin significantly reduce urine output during long dives?
3. Will Desmopressin reduce dehydration and preserve physical and cognitive performance after long submerged operations?

METHODS AND PROCEDURES

This study was conducted with 20 healthy volunteer male subjects who were U.S. Navy divers. All subjects were free of cardiovascular, hematologic, and kidney disease. Subjects provided informed consent to participate. This research was sanctioned by Committees for the Protection of Human Subjects at the Naval Medical Research Institute (NMRI), at the Navy Experimental Diving Unit (NEDU) and at the Naval Medical Research and Development Command (NMRDC). All subjects were asked to adhere to their standard diet. Fluid intake was

ad libitum over the 24 h before starting the pre-hydration phase of the protocol. The subjects did not eat for 6 h prior to the dive. All subjects refrained from strenuous exercise, alcohol, tobacco, caffeine and medications for 24 h before diving. The dives were 3.5 h in duration, using standard SCUBA equipment.

On the morning of the study, subjects drank 10 ml/kg of body weight of tap water 60 min prior to the dive to ensure similar pre-dive hydration between divers. Urine specific gravity was checked to be in the range of 1.015-1.020 to ensure adequate hydration. Aerobic capacity was estimated using the PWC-170 exercise test, a bicycle ergometer test in which the work of pedaling is increased by 0.5 Watts/kg at 1 min intervals until the HR exceeds 150 bpm. The PWC-170 was performed on the day prior to and immediately after each dive. The standard Maximal Oxygen Consumption Test is rigorous and may present excessive stress to a subject immediately after a long dive. Therefore, an approximate maximal oxygen consumption as a HR of 70 bpm was calculated based on projections of the linear relationship between increasing work load and increasing HR using data obtained from our divers prior to diving by methodologies established in our lab (12). Cardiovascular and respiratory variables were monitored on a breath-to-breath basis while subjects performed a pre-determined work schedule. This provided an approximation of maximum oxygen consumption based on methodologies described here (12,22).

Cognitive performance tests also were performed after each dive. Those results were compared to an average of at least 6 baseline control tests performed during the week before the dives. The subject's blood was drawn and a urine specimen obtained 30 min before the dive. They then received either Desmopressin or normal saline intranasally. Subjects were blinded with regard to administration of drug versus placebo. A colorless solution, 0.2 ml in volume, was

administered into each nostril via a flexible calibrated nasal tube. The total dose of Desmopressin administered was 40 μg. Subjects then completed dive preparation consisting of the placement of five skin thermistors, a rectal thermister, and a condom catheter. All thermistors were attached to a depth/time recorder. A dive skin and dry suit were then put on.

Cognitive Measures

Cognitive performance was assessed with a set of measures developed to evaluate the impact of thermal and physical operational stressors (24,25). The cognitive abilities measured were memory, reaction time, vigilance, calculations, logical reasoning and learning; they were measured by matching-to-sample, complex reaction time, visual vigilance, serial addition-subtraction, logical reasoning and repeated acquisition tests. The measures were implemented in a standardized fashion on color display computers used to present stimuli and record responses. A single session of these cognitive performance tasks required approximately 20 min to complete.

Urine Output and Serum Electrolytes

Urine assays were conducted on specimens that were collected within 30 min of diving and immediately after surfacing. Each subject emptied his bladder before diving. A condom catheter was worn inside the dry suit and urine was collected throughout the dive and recorded upon completion of the dive. To simulate normal dive operations, the subjects were asked to refrain from urination as long as possible. Finally, the divers urinated into a container at the end of the dive. This, and the amount collected via the condom catheter represent the total urine output for that dive. Blood samples were drawn within 30 min before diving and within 30 min after surfacing. All exercise and cognitive testing commenced after the blood and urine samples had been taken. Urine analysis and serologic tests were performed at the National Naval Medical

Center (Bethesda, MD) during the pool phase and at the Tyndall U.S. Air Force Base hospital laboratories (Tyndall AFB, FL) during the field phase using standard clinical assays. Values were recorded for sodium (mmol/L), chloride (mmol/L), carbon dioxide (mmol/L), (mg/dL), phosphate, WBC, RBC, hemoglobin (g/dL), hematocrit (%), glomerular filtration rate (GFR) (L/day), urine specific gravity, urine pH, urine osmolality (mosmol), serum osmolality (mosmol) and total urine volume (ml).

Data analysis

Data were analyzed with an analysis of variance (ANOVA) for a complete randomized block design. When the results of the ANOVA were significant, differences among data were detected with the Fisher Least Significance Difference post-hoc test. Values are expressed as means $\pm$ SEM. Statistical significance was achieved at $P < 0.05$.

RESULTS

Urine, Electrolytes and Hematology

Significant differences were noted between several pre- and post-dive measurements in both the placebo and drug conditions during the pool phase (Table I, top). Significantly elevated variables post-dive in the placebo group included: sodium, phosphate, WBC, RBC, hemoglobin, hematocrit, and urine specific gravity. After Desmopressin dives, there were significant elevations only in RBC, hemoglobin, hematocrit and GFR measurements. Post-dive comparisons between placebo and Desmopressin show significant differences in sodium, phosphate, WBC, RBC, hemoglobin, hematocrit, GFR, and urine specific gravity.

Measurements made during the field study demonstrated a significant change only in hematocrit when comparing pre- and post-dive values with placebo. (Table I, bottom). There

were no significant pre- to post-dive differences with Desmopressin. However, when comparing post-dive effects of Desmopressin versus placebo, urine osmolality was significantly elevated. There were no changes in serum osmolality during dives with placebo or Desmopressin, however, administration of Desmopressin resulted in significant reduction in urine volume (Figures 1 & 2). Desmopressin prevented changes in urine electrolytes associated with immersion diuresis and dehydration commonly observed during long dives in warm water. The salient result is that the administration of Desmopressin effectively blocked immersion diuresis while serum osmolality remained unchanged.

Physical Performance

The general pattern of response was the same in both the pool and field portions of this investigation. Desmopressin effectively maintained aerobic capacity after long dives in warm water in both the pool and the field (Figure 3). Aerobic capacity was significantly reduced after both dives with placebo and that reduction was ameliorated by the administration of Desmopressin.

Cognitive performance

There were no significant differences in cognitive performance between any of the comparison groups. Accuracy data from the Matching-to-Sample, Reaction Time, Serial Addition-Subtraction, and Logical Reasoning task, Vigilance Task, and Repeated Acquisition Tasks, were obtained. There were no differences between the pre-dive performance in the placebo versus treatment groups nor were there any differences between the treatment and placebo groups.

DISCUSSION

The most prominent physiologic effect of total body immersion is dehydration resulting from diuresis. Immersion-induced diuresis is caused by central blood shunting resulting from the increased ambient water pressures experienced at depth. This shunting causes increases in left atrial blood pressure resulting in the release of atrial natriuretic protein (ANP) from the right atrium. The blood shunting also reflexly suppresses the release of antidiuretic hormone (ADH) from the pituitary. The result of elevated left atrial pressure is a decrease in serum ADH levels and an increase in ANP levels resulting in immersion diuresis (1,4,5,6,14,18,20,23). The operational Navy is overcoming technological barriers limiting the length of operations, but is now encountering physiologic barriers that limit mission capabilities after extended submerged transits. Many of the performance deficiencies result from the combined effects of fatigue, cold stress and dehydration (13). Desmopressin prevented immersion diuresis and dehydration when administered prior to diving in this study, and was effective at reducing water loss and reduction in body weight during night dives in the operational setting (11). The effect on serum osmolality and total urine volume clearly shows that the intranasal dose of 40 μg was appropriate and blocked both the immersion diuresis and the subsequent dehydration.

The administration of Desmopressin or placebo had no effect on the cognitive performance of the divers during either the pool or open water dives. These findings show that Desmopressin, at the dose administered, can be given to divers conducting shallow warm water dives without concern for its effect on cognitive performance.

There were no decrements in physical performance after dives with Desmopressin, while reductions in physical performance occurred after dives with placebo. Aerobic capacity was maintained in both the pool and field settings when Desmopressin was administered.

In conclusion, Desmopressin at a dose of 40 μg is effective in preventing immersion diuresis and maintaining physical performance during warm water dives in both the laboratory and field setting.

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TABLE I:

Electrolyte and hematologic data collected during the pool phase (top) and field phase (bottom).

POOL STUDY (N = 10)	**PLACEBO**		**DRUG**	
	Pre-Dive	**Post-Dive**	**Pre-Dive**	**Post-Dive**
Sodium	141.5 ± 0.8*	144.3 ± 0.7	140.9 ± 0.6	139.9 ± 0.5**
Hemaglobin	15.3 ± 0.3	16.4 ± 0.3*	15.3 ± 0.3	15.7 ± 0.4
Hematocrit	44.8 ± 0.9	48.5 ± 1.0*	45.1 ± 0.9	46.5 ± 1.1
GFR	180.4 ± 11.3	181.3 ± 11.2	181.8 ± 11.0	194.8 ± 12.7
Urine Spec Grav	1.015 ± 0.003	1.008 ± 0.001*	1.018 ± 0.003	1.016 ± 0.002**
Urine Osmo	634.9 ± 102.3	555.5 ± 295.6	735.9 ± 116.0	742.7 ± 75.4
FIELD STUDY (N = 10)	**PLACEBO**		**DRUG**	
	Pre-Dive	**Post-Dive**	**Pre-Dive**	**Post-Dive**
Sodium	142.0 ± 0.3	142.7 ± 0.9	142.2 ± 0.6	140.5 ± 0.7
RBC	4.8 ± 0.1	5.0 ± 0.1	4.9 ± 0.1	4.9 ± 0.1
Hemaglobin	15.2 ± 0.3	15.9 ± 0.3	15.5 ± 0.1	15.4 ± 0.2
Hematocrit	44.5 ± 0.8	46.4 ± 0.7*	45.3 ± 0.4	45.1± 0.6
GFR	114.4 ± 6.2	118.2 ± 6.9	111.5 ± 6.7	119.1 ± 9.0
Urine Spec Grav	1.017 ± 0.002	1.012 ± 0.002	1.017 ± 0.002	1.038 ± 0.016
Urine Osmo	586.3 ± 97.3	366.6 ± 52.0	664.8 ± 65.1	798.6 ± 47.0**

* Post-dive values different from Pre-dive values, $P < 0.05$

** Post-dive Desmopressin values different from Post-dive placebo values, $P < 0.05$

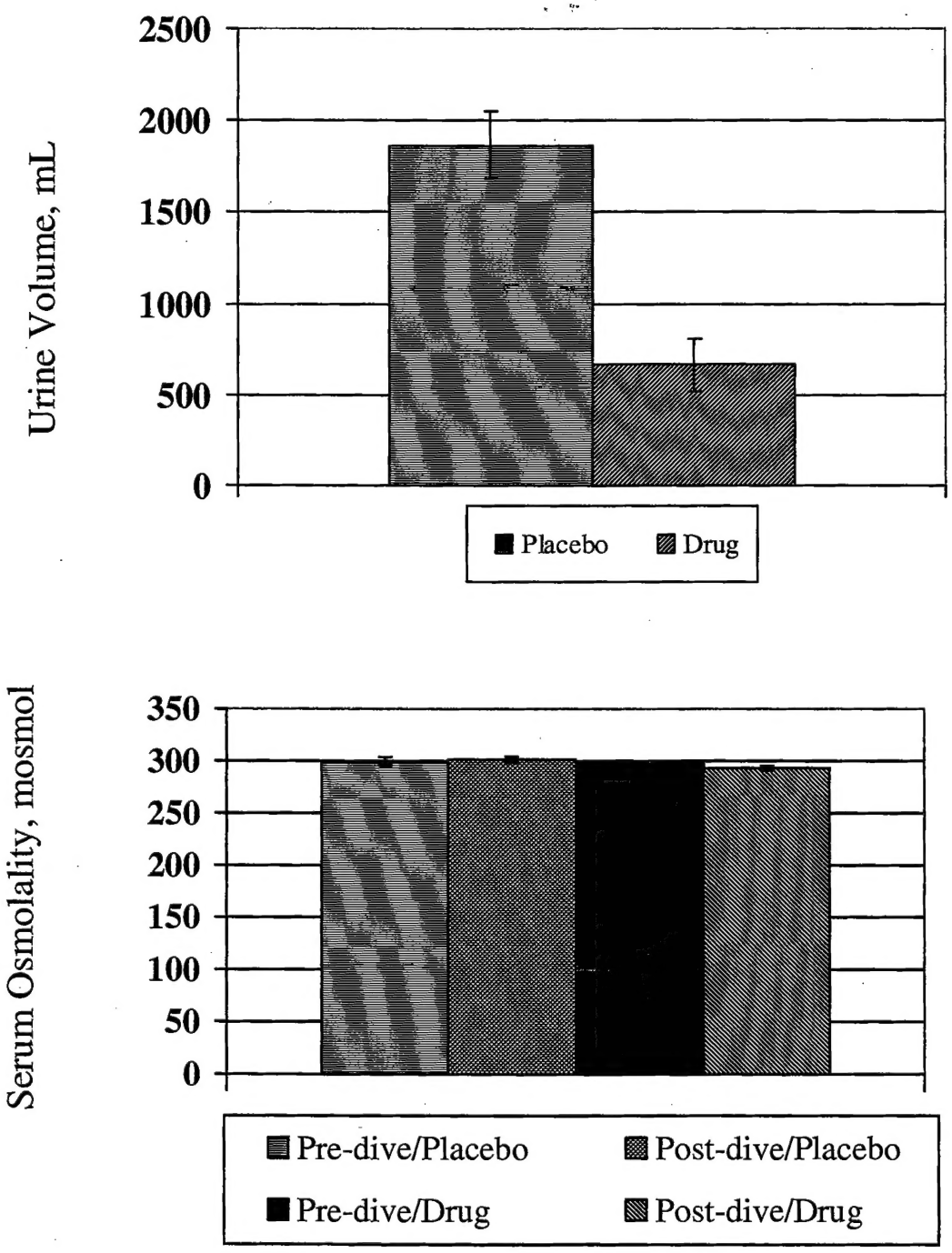

Figure 1. Urine volume (ml) and serum osmolality (mosmol) in the pool phase.

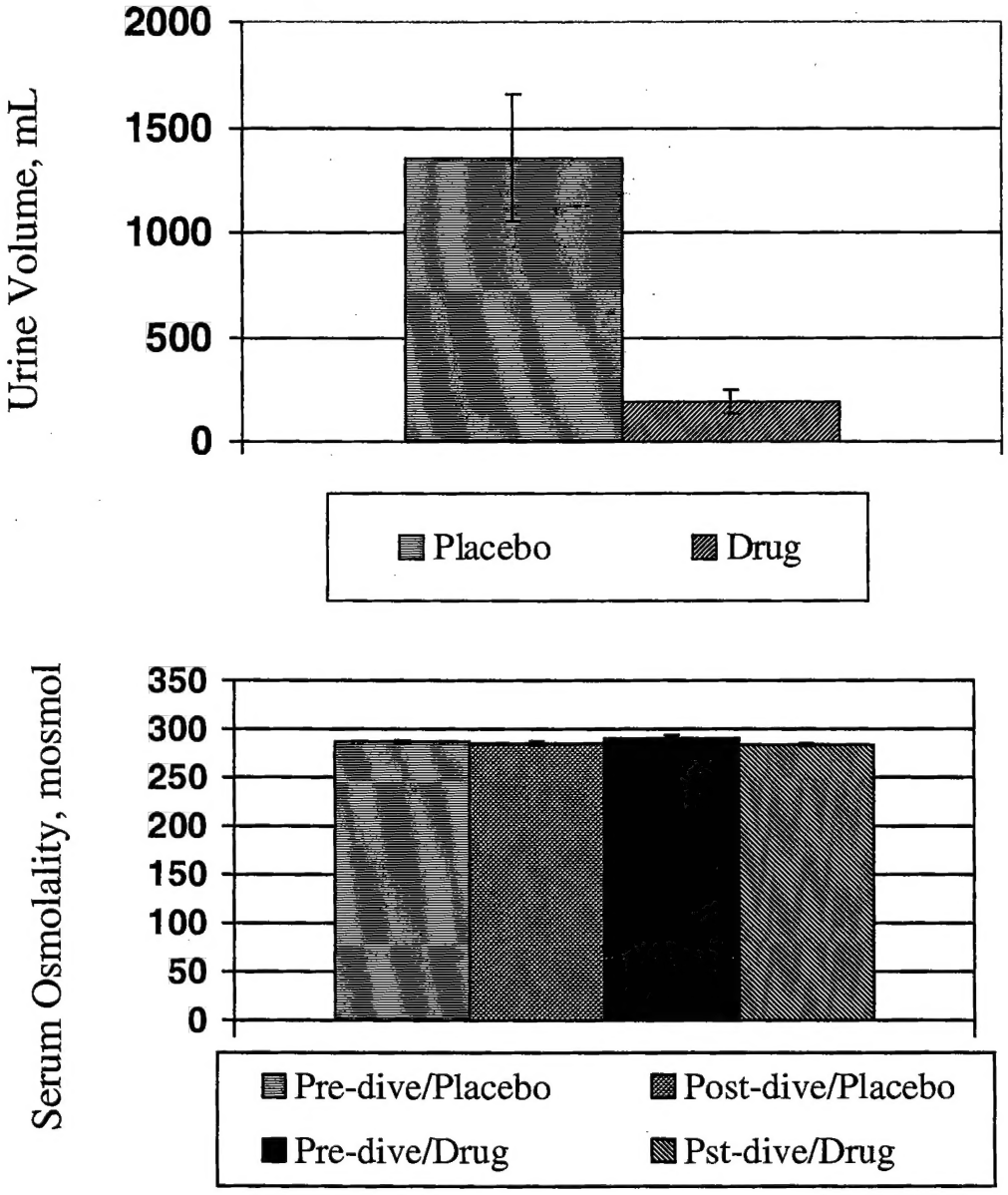

Figure 2. Urine volume (ml)and serum osmolality (mosmol) in the field phase.

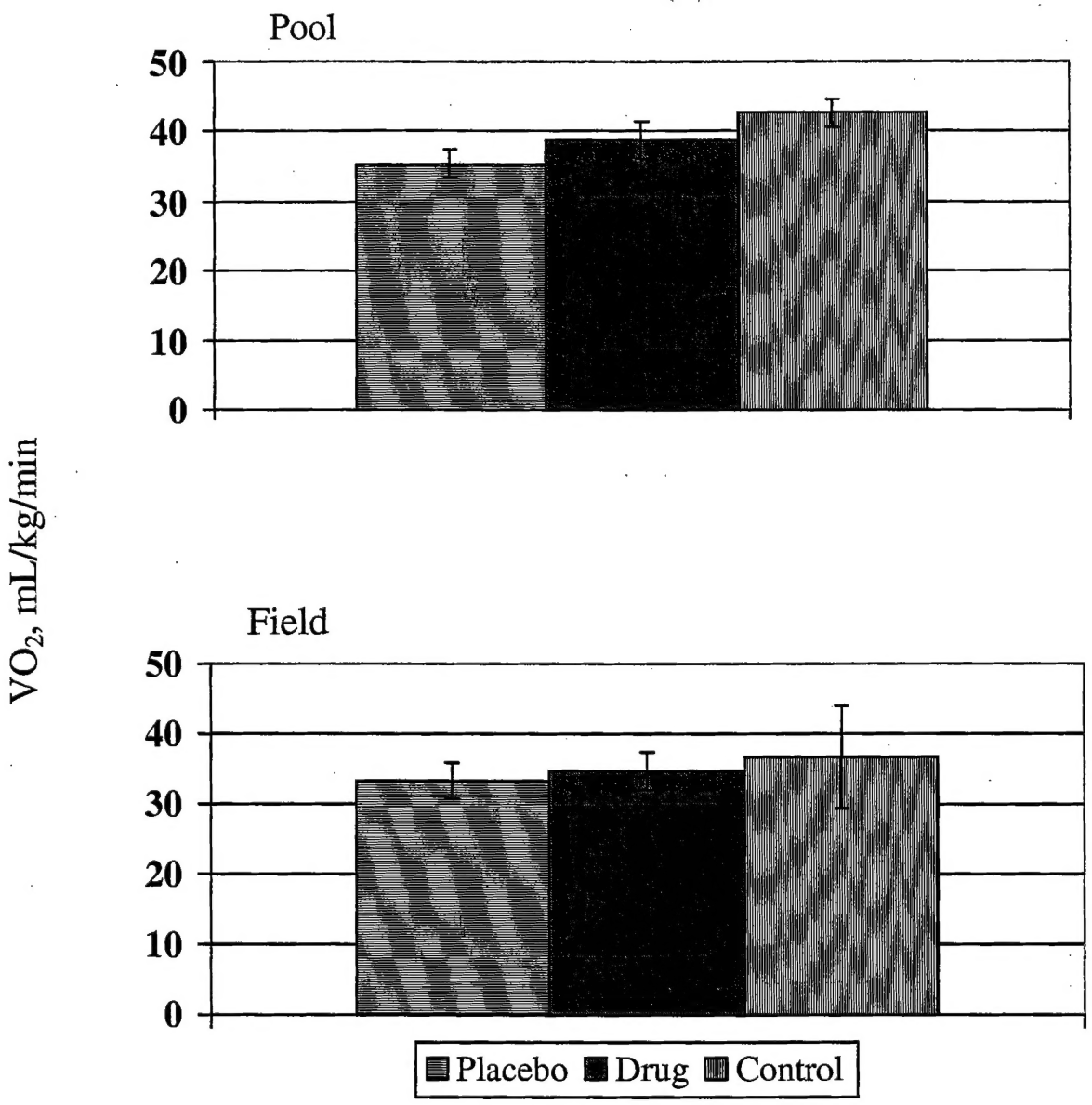

Figure 3. Aerobic capacity (O_2 consumption/kg body wt/min) predicted at a heart rate of 170 as derived from the PWC-170. Results were the same in both settings. Note that aerobic capacity was maintained after dives with Desmopressin, while reduced after diving with placebo.